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From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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WRITTEN OPINION

(PCT Rule 66)

Date of mailing (day/month/year)	11.12.2001
Applicant's or agent's file reference: 15966-557	REPLY DUE: within 1 month(s) from the above date of mailing

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US00/20405	27/07/2000	27/07/1999

International Patent Classification (IPC) or both national classification and IPC
C07K14/50

Applicant
CURAGEN CORPORATION et al.

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ELITE
Annuities

1. This written opinion is the first drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☒	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain document cited
VII	☐	Certain defects in the international application
VIII	☒	Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 27/11/2001.

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WRITTEN OPINION

International application No. PCT/US00/20405

I. Basis f the opinion

1. With regard to the **elements** of the international application (Replacement *sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*):

Description, pages:

1-97 as originally filed

Claims, No.:

1-62 as originally filed

Drawings, sheets:

1/20-20/20 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☐ This opinion has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed.

☐ translation of the earlier application whose priority has been claimed.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 25, 31-33, 44 and 45,

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claim , or said claims Nos. are so inadequately supported by the description that no meaningful opinion

could be formed.

☒ no international search report has been established for the said claims Nos. 25, 31-33, 44 and 45.

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-2, 5-12, 16-19, 21-22, 34-43, 46-56 and 58 (NO)
Inventive step (IS)	Claims	1-24, 26-30, 34-43, 46-62 (NO)
Industrial applicability (IA)	Claims	34-40 and 49-62 (completely) and 26-30 (partially) (see Citatios and explanations).

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

WRITTEN OPINION
SEPARATE SHEET

International application No. PCT/US00/20405

Re Item II
Priority

The priority document of the present application was not available at the time where this preliminary opinion has been drafted. The present analysis is based on the hypothesis that all the claims have a priority right corresponding to the date of filing of the priority document (27.07.99)

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 25, 31-33, 44 and 45 have not been searched by the International Search Authority (ISA). Therefore, claims 25, 31-33, 44 and 45 have not been examined.

Re Item V
Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The present application refers to a Fibroblast Growth Factor (FGF), to nucleic acids encoding it, to vectors comprising said nucleic acids, to host cells comprising said vectors and to antibodies immunospecific for said FGF. The application also refers to methods for identifying compounds modulating the activity of the FGF of the present application and to methods of treatment.

2. **Reference is made to the following documents :**

   D1: DATABASE EMBL [Online] ID: MMFGF9, 8 December 1995 (1995-12-08) SEO: 'Mouse embryonal carcinoma cell mRNA for fibroblast groeth factor 9 (FGF 9), complete cds'

   D2: DATABASE EMBL [Online] ID: FGF9_MOUSE, 1 October 1996 (1996-10-01) SANTOS-OCAMPO ET AL.: 'Glia-activating factor precursor (GAF) (fibroblast growth factor 9) (FGF-9) (HBGF-9)'

   D3: DATABASE EMBL [Online] ID: FGF9_HUMAN, 1 July 1993 (1993-07-01) MIYAMOTO ET AL.: 'Glia-activating factor precursor (GAF) (fibroblast

growth factor 9) (FGF-9) (HBGF-9)'

D4: Advances in cancer research. Vol.59, pp. 115-165 (1992)
Basilico C. and Moscatelli D. : "The FGF family of growth factors and oncogenes".

The document D4 was not cited in the international search report. A copy of the document is appended hereto.

3. **Lack of novelty; article 33(2) PCT.**

Each of the well-known FGFs can be considered as a polypeptide **comprising** an amino acid sequence consisting of a **fragment** of an amino acid sequence given in SEQ ID NO:2 (claim 1) and each of the nucleic acid sequence encoding a well-known FGF can be considered as encoding a polypeptide comprising an amino acid sequence consisting of a fragment of an amino acid sequence as described in SEQ ID NO:2 (claim 6). Moreover, each nucleic acid sequence encoding a well-known FGF can be considered as a nucleic acid molecule **comprising** a nucleotide sequence consisting of a nucleic acid **fragment** of the sequence disclosed in SEQ ID NO:1 (claim 10)

Therefore, the subject-matter of claims 1 and 5-11 can not be considered as novel in the sense of article 33(2) PCT.

The attention of the applicant is drawn to the fact that the wording of claims 2 and 12 encompasses very small peptides and nucleic acid which will not be specific for the FGF-CX polypeptide and nucleic acid of the present application. Such fragments can not be considered as novel in the sense of article 33(2) PCT.

As mentioned above, each FGF polypeptide - which are known to be involved in cell growth and proliferation and, in some cases, to be oncogenes (see D4, p. 144-149, VII Oncogenic potential) - can be considered to fit the definition of claim 1 and the nucleic acid encoding such a nucleic acid can be considered to fit the definition of claims 6 and 10. The therapeutical and diagnostic use of some well-known FGF, fragments thereof, antibodies directed against said polypeptides, or antagonists and agonists of said polypeptides has already been disclosed,

especially for the treatment of cancers. Moreover, FGF nucleic acids have already been cloned in vectors and host cells transformed with said vectors.

Therefore, the subject-matter of claims 16-19, 21-22, 34-43, 46-56 and 58 can not be considered as novel in the sense of article 33(2) PCT.

4. **Lack of inventive step; article 33(3) PCT.**

The document D4 has been considered as the most relevant document for the evaluation of the inventiveness of the claims.

D4 discloses the structures and functions of several FGFs and their role in oncogenesis. D4 mentions the biological function of FGFs including the role of the FGFs in angiogenesis (p. 140-144, VI. Biological function, last paragraph) and the identification of some FGFs as oncogenes (p. 144-149, VII Oncogenic potential). The involvement of FGFs in tumors is also discussed (p. 149-155, VIII. Involvement of FGFs in tumors).

In view of the teaching of D4, the problem to be solved by the present application is the provision of a further fibroblast growth factor.

The application solves said problem by the provision of the human FGF-CX polypeptide and nucleic acid.

The IPEA is the opinion that, knowing that the fibroblast growth factors belongs to the largest family of growth factors (D4, p. 115, I. Introduction, lines 2-3), the isolation of a novel FGF, using as a probe the nucleic acid sequence of well-known FGFs (like FGF-9 which was well-known at the priority date of the present application), could only be considered as inventive if the selection of the FGF-CX is motivated by a technical effect, i.e. a hitherto unknown or unexpected effect due to the selection of the specific FGF-CX of the present application.
For the moment, the IPEA fails to see such an effect for the FGF-CX of the present application.

Therefore, claims 1-17 can not be considered as inventive in the sense of article

33(3) PCT.

Moreover, the IPEA is the opinion that the skilled person, knowing that some well-known FGFs have been implicated in diseases or the treatment or diagnostic of diseases like cancers would have needed no inventive activity to consider using the non-inventive FGF-CX polypeptides, nucleic acids, agonists or antagonists of said polypeptides and antibodies directed against said polypeptides in the treatment or diagnostic of cancers or other FGF-associated diseases.

Therefore, the subject-matter of claims 18-62 don't appear to be inventive (article 33(3) PCT).

For the discussion about inventive step :

The attention of the applicant is drawn to the fact that several well-known FGFs have been shown to be involved in brain development. Moreover, the treatment methods of the present application are based on functions common to all FGFs rather than on a specific function linked to the FGF-CX polypeptide.

5. Industrial applicability; article 33(4) PCT.

The methods of claims 34-40 and 53-62 are methods of treatment of the human or animal body and the methods of claims 49-52 are methods of diagnostic practised on the human or animal body.
Moreover, the methods of claims 26-30 can be considered as methods of diagnostic practised on the human or animal body as far as they are practised in vivo.
For the assessment of the present claims 34-40 and 49-62 (completely) and 26-30 (partially) on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

WRITTEN OPINION
SEPARATE SHEET

International application No. PCT/US00/20405

Re Item VIII
Certain observations on the international application

Lack of clarity; article 6 PCT

1. As a first remark concerning the claims of the present application, the attention of the applicant is drawn to the fact that, according to the PCT Gazette of the 29.10.98 "PCT International Preliminary Examination Guidelines", Chapter III-5.1 : "The requirement that the claims shall be concise refers to the claims in their entirety as well as to the individual claims. The number of claims must be reasonable when considered in relation to the nature of the invention claimed, and undue repetition of wording, for example between one claim and another, should be avoided by the use of the dependent form". The IPEA is the opinion that, in the case of the present application, the number of claims could be easily reduced.

2. Claims 3, 7 and 8 refer to a naturally occurring allelic variant of the polypeptide or nucleic acid of the present application. The attention of the applicant is drawn to the fact that there is no clear definition of what such an "allelic variant" should be what renders the scope of the corresponding claims unclear.

3. Claim 12-15 refer to a FGF-CX polypeptide or variants or fragments thereof. The attention of the applicant is drawn to the fact that the term "FGF-CX" is an internal designation meaningless for the skilled person.
According to Article 6 PCT in combination with Rule 6.3 PCT, the claims shall define the matter for which protection is thought in terms of technical features. The IPEA is of the opinion that a peptide, polypeptide, protein, oligonucleotide, gene, etc... being chemical products must be clearly and unambiguously characterized by their amino acid and/or nucleic acid sequences, i.e. by reference to their specific SEQ ID No. The characterization of a product only by the desired function or by an arbitrary abbreviation or designation without any real technical meaning does not seem to fulfill the requirements of said Article 6 PCT in combination with Rule 6.3 PCT. Thus, the IPEA is the opinion that the FGF-CX polypeptide of claims 12-15 should be defined by reference to its specific peptide sequence.

4. The method of claim 38 refers to the administration of a Therapeutic to a subject. There is no definition of what such a "Therapeutic" could be what renders the scope of the claim unclear.